PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P745-PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/JP2004/006211	International filing date *(day/month/year)* 28.04.2004	Priority date *(day/month/year)* 28.04.2003
International Patent Classification (IPC) or national classification and IPC A61K39/505, A61K39/395		
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.09.2004	08.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Wagner, R Telephone No. +49 89 2399- 7357

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/006211

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-40 as originally filed

   Claims, Numbers

   1-80 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-5 (in part), 28-32 (in part), 55-59 (in part), 55-80 (IA)

because:

☒ the said international application, or the said claims Nos. 55-80 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-5 (in part), 28-32 (in part), 55-59 (in part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	22-27,49-54,75-80
	No:	Claims	1-21, 28-48, 55-74
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-80
Industrial applicability (IA)	Yes:	Claims	1-54
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item II
Priority

As the priority document of the present application is not available at the moment of the present preliminary examination, and thus considered as being valid, the non-patent documents identified as PX in the International Search Report are considered as not forming part of the prior art.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The scope of claims 1-5, 28-32, 55-59 is not clear (Article 6 PCT) because the interleukin-6 antagonists is a functional definition which does not allow to determine which substances fall within the scope of said claims. In order to determine the scope of the claims the skilled person is faced with the undue burden to test all existing and even not yet discovered compounds in regard to their inhibitory function on IL-6.
   The search and the present examination is therefore limited to the interleukin-6 antagonists (page 8, lines 32-34): anti-IL-6 antibodies, anti-IL-6R antibody, anti-gp 130 antibody, modified IL-6, modified soluble IL-6R, partial peptides of IL-6 or IL-6R. The low molecular weight substances (page 8, line 35) do not represent a meaningful limitation which would allow the skilled person to determine which further compounds are included in the scope of the claims, therefore small molecules are also excluded from the search and examination.

2. Claims 55-80 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:
D1: US5210075
D2: Choy et al., Arthritis and Rheumatism, Vol. 46, No. 12, 2002, pp.3143-3150
D3: Nishimoto et al., Abstract 199, page S84, vol. 44, issue S9, Arthritis and Rheumatism
D4: EP1074268
D5: WO9710338
D6: WO9964070

1. For the assessment of the present claims 55-80 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2. Claims 4,5,31,32,58,59 are limited by the concept of high dose. Said feature is relative and vague (Article 6 PCT) and does not represent a limitation to the scope of said claims.

3. Claims 29 and 30 are not clear (Article 6 PCT). The wording of said claims does not allow to determine which compound is actually enhancing (claim 29) or reducing the allergic reaction. Claim 29 is interpreted as being to the use of an IL-antagonist and an immunosuppressant for the production of a pharmaceutical composition for the treatment of IL-6 related diseases. It must be underlined, that the treatment of IL-6 related diseases does not represent a limitation of the use.

   Claim 30 is interpreted as being to the use of an immunosuppressant for the production of a pharmaceutical composition for the reduction or prevention of allergic reactions against IL-6 antagonists.

4. D1 discloses the use of interleukin-6 antagonist peptides in combination with immunosuppressants for the treatment of IL-6 mediated diseases, like rheumatoid arthritis (columns 23, 29). As the co-administration of the immunosuppressants inherently increases the anti-inflammatory effect of an anti-IL6 antagonist and inherently reduces a possible immune reaction against an administered antibody, the subject-matter of claims 1-5, 28-32 (see also section 3), 55-59 and 15, 42, 68 is not novel (Article 33(2) PCT).

5. D2 discloses a treatment of rheumatoid arthritis by using a anti-IL-6 receptor antibody (MRA). One group of patients receives a dose of 10 mg/kg of MRA and the patients were allowed to take prednisolone at a daily dose inferior to 7.5 mg. Therefore D2 anticipates the subject-matter of claims 1-10, 13, 15-22,28-37, 40, 42-48, 55-63, 66, 68-74 (Article 33(2) PCT). D2 does not disclose whether the MRA antibody is administered simultaneously with the prednisolone or not . As the administration schedule of the anti IL6-R antibody and the immuno-suppressant does not have any surprising effect, the subject-matter of claims 26, 27, 53, 54, 79, 80 does not involve an inventive step with regard to D2 (Article 33(3) PCT).

6. D3 discloses a clinical study in which an anti-IL6R antibody is administered at a dose of 2, 4 or 8 mg/kg/2 weeks for the treatment of rheumatoid arthritis. Therefore the D3 anticipates the subject-matter of claims 4-10, 13, 15, 31-37, 40, 42, 58-63, 66, 68 (Article 33(2) PCT).

7. D4 discloses anti-IL6 R antibodies PMI and MR16-1 [0034] to be administered at doses between 0.01 and 100 mg/kg [0117] for the treatment of ulcerative colitis or Crohn's disease. As the concept of high doses is relative and cannot be regarded as a distinctive feature, D4 anticipates the subject-matter of claims 4-15, 31-42, 55-68 (Article 33(2) PCT).

8. D5 (page 22) discloses a combination therapy with IL-6 receptor antagonists (IL-6 muteins) and anti-TNF antibodies in the treatment of sepsis. Anti-TNF antibodies are immunosuppressants according to the description (infliximab, page 7, line 5) and therefore D5 anticipates the subject-matter of claims 1, 2, 3, 4, 5, 28-32, 55-59 (Article 33(2) PCT). D6 (page 6, line 11) discloses a combination of anti-IL6 antibodies and anti-TNF antibodies for the treatment of sepsis, therefore D6 anticipates the subject-matter of the same claims.

9. The subject-matter of claims 22-25, 49-52, 75-78 is novel because the prior art, published prior to the priority date (considered to be valid) of the present application does not disclose the combination of an "IL-6 antagonist" and methotrexate. D2 is to be considered as the closest prior art in which the treatment of rheumatoid arthritis by anti-IL6 receptor antibodies is disclosed. The difference between the present claims 22, 49 and 75 and the disclosure of D2 resides in the fact that in the present claims methotrexate is combined to the antibodies. The technical problem to be solved is the choice of a combination partner for the anti-IL6 receptor antibody, which would achieve a synergic effect (page 2, lines 32-34 of description) or which would reduce or prevent allergic reaction, i.e. antibody formation, against the IL6-R antibody. As the present application does not disclose any data showing that one of the effects has been achieved, an inventive step cannot be acknowledged for the subject-matter of claims 22-25, 49-52, 75-78 (Article 33(3) PCT).

Further Remarks:

10. In claims 11, 12, 14, 38,39,41,64,65,67 antibodies are designated by internal denominations. In order to avoid a lack of clarity said antibodies should be identified by their respective deposit accession numbers cited on page 10 of the description.

11. Claims 25, 26, 53 and 54 are not clear (Article 6 PCT) because they refer to an anti-IL6 antibody, but are dependent on claims directed to anti- IL6 receptor antibodies.

12. The expression "immunosuppressants" is not clear (Article 6 PCT) because the skilled person is not aware of a possible immunosuppressant effect of all existing compounds.

Re Item VI

Certain documents cited

Certain published documents might be relevant for novelty in a future regional/national phase.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/JP2004/006211

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 04/039826	13.05.2004	26.10.2002	26.10.2002